Environmental Exposures and Genetic Variation Interactions and Asthma

Environmental exposures interact with **genes** to increase the **risk of asthma** and wheezing in children.

General Information	
Broad Focus Area	Asthma
Background and Justification	Childhood "asthma" can be categorized into three phenotypes: 1) airway obstruction which begins in the first two years of life but does not persist to school age, often referred to as early onset transient airway obstruction; 2) early-onset airway obstruction that persists past school age, or early-onset persistent asthma; and 3) recurrent airway obstruction that begins after the first few years of life, or late-onset asthma.[1] Few studies have examined asthma risk according to these three phenotypes. Prospective data are needed to examine risk factors for the development of these phenotypes and examine risk factors for persistence of airway obstruction into later childhood and adulthood. Family data has clearly identified an important genetic component to asthma. While the specific genes or interaction between genes are not yet known, this is an active area of investigation, and there are a large number of plausible candidate genes. For each of these asthma phenotypes, interactions between genetic and environmental factors need to be explored. While asthma genes likely interact with environmental factors, there is little work on gene-environment interaction in asthma. For example, data from human exposure studies indicates that individual susceptibility is important in the respiratory response to air pollutants, including ozone[2] and endotoxin.[3] Genes involved in response to endotoxin have been identified in humans,[4] and work in mice has identified linkage regions important in response to ozone[5] and particulate air pollution.[6]
Prevalence/ Incidence	Nine million children less than 18 years of age are estimated to have asthma.[7] Among children, it is the most common chronic illness.[8] The prevalence of asthma increased from 35 to 62 per 1,000 children aged 0 to 17 years between 1980 and 1996.[9]
Economic Impact	In 1997, the annual estimated cost of pediatric asthma in the US was $6.6 billion.[10] By 2002, the total cost of asthma was estimated at $14 billion.[11] The more severe forms of asthma account for a disproportionate amount of the total direct costs; one study estimated that less than 20% of asthmatics account for over 80% of the direct costs.[12] Asthma also poses a substantial and increasing public health burden in lost time from school and usual activities and in health care utilization.

Exposure Measures			Outcome Measures	
Primary/ Child	Genetics: - Family history of allergy, asthma, and respiratory illness; family immune history Environmental exposures (home, school and daycare): - Environmental samples (e.g., mold, endotoxins, allergens, environmental tobacco smoke) - Other exposure information		***Primary/ Child***	Asthma: - allergic sensitization - airway reactivity - immune system function (e.g., lymphocytes, cytokines, IgE, interleukins)

	(housing characteristics, product usage in home, parental occupational/hobby data, food/diet questionnaire, child time activity patterns (GPS))			
Methods	- Interview/questionnaire - Medical record review - Blood for genotype - Physical sampling (air, dust) of home, school, and daycare		Methods	- Examination and interview by medical professional (e.g., skin sensitivity test) - Medical record review - Blood samples
Life Stage	Periodic, birth through year 20		Life Stage	Periodic, birth through year 20

Important Confounders/Covariates	
Maternal stress and infection during pregnancy	Maternal stress and infection during pregnancy may increase risk of asthma.[13, 14]
Early childhood infections	Early childhood infections may increase risk of asthma, due to an additional burden of airway obstruction.[15]
Nutrition	Poor nutritional status may increase the risk of asthma and wheezing in children with certain genetic components, but not all of these phenotypes have been identified.[16]

Population of Interest		Estimated Effect that is Detectable
Children with medically diagnosed asthma		The smallest detectable relative risk is approximately 1.2. This power estimate assumes a sample size of 100,000 at age of diagnosis, an asthma incidence of 5%, and a cut-off value for "high" exposure based on the upper 5th percentile of NCS subjects (i.e., a proportion exposed of 0.05). It assumes only a main effects model based on exposure to a single factor (e.g., a single pollutant) without consideration of interactions with other exposures, genetics, family history, etc.[17]

Other Design Issues	
Ethical/Burden Considerations	There may be ethical considerations associated with genetic tests, but such considerations underlie the overall NCS and would not be unique to this specific hypothesis. For non-genetic factors, the study will need to have a formal strategy and process for an effective communication of the results of physiological and biochemical measures to the child's parents and to a responsible health care provider. The study also will need to have a formal strategy and process for effective communication of the results of environmental monitoring to the child's parents along with appropriate and feasible recommendations regarding the correction of any unhealthful environmental findings. In addition, a mechanism needs to be identified to ensure that children found to have asthma through this study can receive adequate medical care for their illness. Repeated assessments can be burdensome.
Cost/Complexity of Data Collection	Potentially time-consuming and costly to implement environmental

	and other assessments. Effects at later life-stages may be more difficult to detect due to attrition of study subjects.
Need for Community Involvement	Daycare and school cooperation would be required for some of the intended environmental exposure measures.

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